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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 24

Application Number: 09/382,622
Filing Date: August 25, 1999
Appellant(s): DEES ET AL.

Edward D. Manzo and Mark J. Murphy
For Appellant

This is in response to the appeal brief filed March, 21 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after non-final office action in Paper No. 19, contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 10, 51 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

SERAFINI A.N. "Iodine-123-Rose Bengal: An Improved Hepatobiliary Imaging Agent", Journal of Nuclear Medicine, vol. 16, no. 7 (1975), pp. 629-632.

NECKERS D.C. "Rose Bengal", Journal of Photochemistry and Photobiology. A Chemistry (1989) vol. 47, pp. 1-29.

US 5,780,052 KHAW et al. 7/1998

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A) Claims 1-3 and 5-8 stand rejected under 35 U.S.C. 102(b) as being inherently anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975) for reasons of record in Paper No. 19 and reiterated as follows.

Serafini et al. teach a halogenated, i.e. iodinated, xanthene, in this case, Rose Bengal, which is principally tetrachlorotetraiodofluorescein. Rose Bengal allows for 1) rapid and efficient incorporation into molecules so as to attain overall reduction in imaging time and radiation exposure, and 2) improved images (see Abstract). Serafini et al. use the agent for treating diseased tissue as a radiopharmaceutical agent. In a

study, Serafini et al. intravenously injected Rose Bengal into healthy volunteers, blood clearance and urinary clearance studies were performed, then simultaneous and sequential scintiphotos were taken of the cardiac, liver, biliary, and intestinal systems. It was found that sufficient concentration of Rose Bengal into diseased tissue, i.e. localization, within the liver then the rest of the biliary tree of the radiopharmaceutical agent is observed with marked improvement in anatomic detail showing specific areas of radioactive concentrations (see page 630, column 2). In sum, Serafini et al. teach Rose Bengal, a halogenated xanthene, and further teach of its characterization as being capable of being activated and/or ionized by radiation. As such, Rose Bengal, when activated by ionizing radiation, has the inherent capability to enhance therapeutic efficacy for treatment of cancer and tumors. The discovery of a new property for use of a known compound does not render the compound novel. It is, therefore, maintained that recited claims 1-3 and 5-8 are inherently anticipated by Serafini et al.

B) Claims 1-3 and 5-9 stand rejected under 35 U.S.C. 102(b) as being inherently anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) for reasons of record in Paper No. 19 and reiterated as follows.

Neckers teaches and describes halogenated xanthenes such as Rose Bengal or 2,4,5,7- tetraiodo-3', 4', 5', 6'- tetrachlorofluorescein. Neckers specifically teach that Rose Bengal and Eosin have distinct spectral, photochemical, and photophysical properties. Neckers teaches that Rose Bengal, disodium salt is characterized 1) as a photodynamic sensitizer, 2) by large absorption in all solvents, 3) by its capacity to be

activated as an imaging agent, i.e. shows fluorescence, 4) by a triplet that is completely quenched by oxygen, 5) by its concentration on selected tissues, i.e. tumor: its spectrum is most diagnostic of its immediate environment, 6) by bleaching in protic, polar solvents, (7) by its singlet quenched by strong oxidizing agents (see page 1). The absorption and emission spectra of certain Rose Bengal derivatives are enumerated in Table 2 and 3, respectively. In sum, Neckers teaches Rose Bengal, a halogenated xanthene, and further teach of its characterization as being capable of being activatable and/or ionized by radiation. As such, Rose Bengal, when activated by ionizing radiation, has the inherent capability to enhance therapeutic efficacy for treatment of cancer and tumors. The discovery of a new property for use of a known compound does not render the compound novel. It is, therefore, maintained that recited claims 1-3 and 5-9 are inherently anticipated by Neckers.

C) Claims 4, 15, and 18-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Khaw et al. (US 5,780,052) for reasons of record in Paper No. 19 and reiterated as follows.

Serafini et al. and Neckers are discussed supra. Serafini et al. and Neckers differ from the instant invention in failing to disclose incorporating the halogenated xanthenes into specific delivery systems for enhanced targeting towards specific localized tissues.

Khaw et al. disclose a method of enhancing effects of therapy that kills diseased (malignant/tumor) cells in vivo by providing (immuno)liposomes specific for an internal cellular antigen present in degenerating neoplastic cells. Techniques are known for liposome targeting such as conjugating antibodies to cell-surface (malignant) antigens to pharmacologically active agents and labels to permit diagnosis, localization, and therapy toward tumors (see column 7, line 48 to column 8, line 3). The liposomes contain antineoplastic agent for initiating therapy in a mammal to kill malignant cells in vivo (see column 2, last paragraph). The antineoplastic agents include radiosensitizing agents, cytotoxic agents, and radionuclides (see column 3, first paragraph and column 4, lines 18-27). In diagnostic procedures, (immuno)liposomes containing radiosensitizer and diagnostic agent which are specific for intracellular antigens, such as an imaging agent, are injected into a patient receiving radiation therapy. Following administration, an imaging technique is employed such as computed axial tomography (CAT) scan and X-ray imaging (see column 16, line 18 to column 17, lines 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the radiosensitizer agent taught by Serafini or Neckers using liposomal targeting technique as taught by Khaw because Khaw specifically taught that pharmaceutically of therapeutically activatable agents can be incorporated into liposomes or other delivery systems, for targeting delivery to malignant tumors in vivo which allows for localization of the agent into targeted specific tissues.

D) Claim 10, 51, 52, 56-57, and new claims 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Norman et al. (Invest Radiol, 26: S120-S121, 1991) for reasons of record in Paper No. 19 and reiterated as follows.

Serafini et al. and Neckers are discussed supra. Serafini et al. and Neckers differ in failing to teach activating the radiosensitizer agents with ionizing radiation at specific parameters: greater than or equal to 1 keV and less than or equal to 1000 MeV.

Norman et al. teach a radiosensitizer agent, i.e. iodinated contrast medium such as gandolinium, for treatment of diseased tissue by activating the agent with ionizing radiation wherein doses absorbed from diagnostic X-rays are enhanced. Norman et al. specifically teach that the radiosensitizer agent exhibits preference to localize at biologically sensitive diseased tumor tissues. In experimentation, Norman et al. showed that survival of rabbits increased when irradiation therapy was preceded by injection of the iodinated contrast media (see page S120, column 1, paragraph 1). Norman et al. also teach that dose enhancement factor (DEF) which increases linearly with the concentration of iodine can be achieved with other conventional ways of administering the contrast media (S120, column 1 and 2). Figure 1 shows a plot of the DEF as a function of the iodine concentration in a lymphocyte medium during irradiation at 140 keV. In conclusion, the therapeutic ratio, the ratio of radiation dose absorbed by a diseased brain tumor tissue versus that absorbed by the surrounding normal brain tissues increases with increasing iodinated contrast media in the diseased tissue.

One of ordinary skill in the art at the time of the instant invention would have been motivated to activate the iodinated contrast medium, i.e. Rose Bengal, taught by Serafini and Neckers, with ionizing radiation at 140 keV as taught by Norman because Norman specifically taught that gandolinium, which is another iodinated contrast medium, exhibits preference to localize at biologically sensitive diseased tumor tissues when ionized at 140 keV and the Rose Bengal taught by Serafini and Neckers, appears to be an obvious variation or modification of an iodinated contrast medium used as imaging agent, and which have been taught by Serafini and Neckers as being characteristically capable of photodynamic and radiation activation.

Allowable Subject Matter

E) The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Khaw et al. (US 5,780,052) is, hereby, withdrawn.

As discussed with Appellant's representative, claim 14 which is understood to be a derivatized halogenated xanthene, i.e. halogenated xanthene attached to a biological targeting moiety, for use in enhancing targeting to biologically sensitive structures of cancer or tumors, is allowable since such is structurally distinct from the known compound taught by the prior art.

In the phone interview on 7/16/02, however, the Appellant was grateful about an offer of allowance but graciously declined, in favor of taking the claims, as currently recited, to the board.

(11) Response to Argument

A) Appellant argues that the claims are not directed merely to halogenated xanthenes and concede that halogenated xanthenes are known substances (see Appeal Brief at page 18, first full paragraph). Appellant contends that the claims, instead, are directed to a specific class of medicinal compositions which include halogenated xanthenes and ionizing radiation. According to Appellant, the agents in the present invention are "medicinal drugs" that can be administered to patients, i.e. medicinal purposes, to improve efficacy of radiation therapy. The existing reagent grade commercial product, i.e. reagent grade Rose Bengal, used in industrial laboratory is completely distinct from the claimed drug used in radiation therapy, as a radiosensitizer for treatment of cancers and tumors comprising halogenated xanthene which interacts with ionizing radiation applied to cancer or tumor.

In response, the discovery of a new property of known compounds or product, in this case, halogenated xanthenes such as Rose Bengal, discovered to characteristically enhance efficacy of ionizing radiation applied to cancer or tumor in radiation therapy, does not render the product novel, unless otherwise, rendered novel or nonobvious from a modification or variation of its original structure, i.e. "ionized Rose Bengal" or "derivatized Rose Bengal with a biological targeting moiety", that is structurally different,

novel, and nonobvious, i.e. with different pH (as an example) from all other commercially known Rose Bengal. Further, a recitation of the intended use of the claimed product must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

B) Appellant argues that the claims are directed to novel and nonobvious combinations of 1) radiosensitizer agent comprising a halogenated xanthene, 2) interacting with ionizing radiation applied to a cancer or tumor, 3) to enhance therapeutic efficiency of the ionizing radiation. Appellant argues that none of the cited references, specifically Serafini et al. disclose or suggest that a halogenated xanthene or Rose Bengal is a radiosensitizer or radiosensitizer agent for interacting with ionizing radiation.

In response, Examiner concurs that Serafini et al. does not disclose use of Rose Bengal and other halogenated xanthenes as a radiosensitizer agent interacting with ionizing radiation to treat cancer or tumor. Examiner concurs that Serafini et al.'s use is completely different from that in claim 1. The recited claims, however, do not appear to be drawn to method of using Rose Bengal as radiosensitizer agent, i.e. for treatment of cancer and tumors upon interaction with ionizing radiation to enhance therapeutic efficacy of the ionizing radiation. Instead, the claims are drawn to the halogenated

xanthenes as products, specifically Rose Bengal, which Appellant admits in this Brief at page 18, first full paragraph that they are known substances in the art. The Rose Bengal taught by Serafini et al., albeit used for another purpose, is nevertheless, the same Rose Bengal as that claimed by Appellants, upon which ionizing radiation is applied for activation; there is no structural difference to render it novel and distinct. Absent evidentiary showing that the structure of the Rose Bengal taught by Serafini et al. distinctly differs from the claimed invention, absent evidentiary showing that the Rose Bengal as taught by Serafini et al. would not have exhibited the same capability to treat cancer or tumor upon exposure to ionizing radiation, it is maintained that the Rose Bengal taught by Serafini et al. is the same compound as the "radiosensitizer agent" taught in the claimed invention.

C) Appellant argues that Neckers does not teach or suggest the agent of the claimed invention as a radiosensitizer agent for use with radiosensitization or ionizing radiation in the treatment of cancer or tumors. Appellant argues that Neckers' teaching of use in optical radiation of Rose Bengal is completely different from the use with ionizing radiation as radiosensitizer agent of claim 1.

In response, Examiner concurs that Neckers does not disclose use of Rose Bengal and other halogenated xanthenes as a radiosensitizer agent interacting with ionizing radiation to treat cancer or tumor. Examiner concurs that Neckers only describes halogenated xanthenes and provides features and characterization of halogenated xanthenes. Alternatively, the recited claims do not appear to be drawn to a

novel method of using Rose Bengal with ionizing radiation applied to cancer and tumors to increase efficacy of the radiation therapy. Instead, the claims are drawn to the halogenated xanthenes as products, specifically Rose Bengal, which Appellant admits in this Brief at page 18, first full paragraph that they are known substances in the art. The Rose Bengal taught by Neckers, albeit silent in teaching application of ionizing radiation thereto, is nevertheless, characteristically the same Rose Bengal as that claimed by Appellants, the same Rose Bengal upon which ionizing radiation is applied for activation in radiation therapy; there is no structural difference to render it novel and distinct. Absent evidentiary showing that the structure of the Rose Bengal taught by Neckers distinctly differs from the claimed invention, absent evidentiary showing that the Rose Bengal as described by Neckers would not have exhibited the same capability to treat cancer or tumor upon exposure to ionizing radiation, it is maintained that the Rose Bengal taught by Neckers is the same compound as the "radiosensitizer agent" taught in the claimed invention.

D) Appellant argues that the combination of Serafini et al. or Neckers with Khaw et al. does not suggest the "radiosensitizer agent" of the claimed invention which is halogenated xanthene or Rose Bengal upon which ionizing radiation is applied for treatment of cancer or tumors. Appellant argues that Khaw et al. does not correct the deficiencies of Serafini et al. and Neckers by rendering obvious the "radiosensitizer agent" recited in claim 1. According to Appellant, Khaw et al. only discloses delivery systems comprising immuno-complexed liposomes which deliver contrast agents or

radioopague agents to target tissues. However, Khaw et al. does not teach or suggest halogenated xanthenes or simple delivery systems such as simple liposomes as recited in the claims.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Serafini et al. and Neckers references were combined with Khaw et al. in an obviousness rejection. Examiner concurs that Serafini et al. or Neckers combined with Khaw et al., does not suggest using halogenated xanthenes with ionizing radiation as a radiosensitizer agent for enhancing radiation therapy in treating cancer or tumor. However, the recited claims do not appear to be drawn to a novel method of using Rose Bengal with ionizing radiation applied to cancer and tumors to increase efficacy of the radiation therapy. Instead, the claims are drawn to the halogenated xanthenes as products, specifically Rose Bengal, which Appellant admits in this Brief at page 18, first full paragraph that they are known substances in the art. The teaching of the combination of Serafini or Neckers with Khaw, albeit silent in suggesting capacity of halogenated xanthene to enhance radiation therapy upon application of ionizing radiation, nevertheless, suggests delivery into tissue of characteristically the same Rose Bengal as that claimed by Appellants, the same Rose Bengal upon which ionizing radiation is applied for activation in radiation therapy; there is no structural difference to render it novel and distinct. Absent evidentiary showing that the structure of the Rose Bengal taught by Serafini et al. and

Neckers which is incorporated into liposomes as suggested by Khaw et al., distinctly differs from the claimed invention, absent evidentiary showing that the Rose Bengal aforementioned, would not have exhibited the same capability to treat cancer or tumor upon exposure to ionizing radiation, it is maintained that the Rose Bengal taught by Serafini et al. or Neckers is the same compound as the "radiosensitizer agent" taught in the claimed invention.

E) Appellant argues that the combination of Serafini et al. or Neckers with Norman does not suggest the "radiosensitizer agent" of the claimed invention which is halogenated xanthene or Rose Bengal upon which ionizing radiation is applied for treatment of cancer or tumors. Appellant argues that Norman does not correct the deficiencies of Serafini et al. and Neckers. Appellant argues that Norman teaches another "exotic" radiodense compound, gandolinium, upon which ionizing radiation is applied for enhancing radiation therapy. Appellant specifically argues that gandolinium is not a halogenated xanthene and further argues that Norman teaches use of complex radiosensitizer / nucleic acid conjugates for enhanced incorporation into target cells which is a difficult delivery system in comparison to injecting. As such, Appellant contends that Norman teaches away from the claimed invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Serafini et al. and Neckers references

were combined with Norman in an obviousness rejection. Examiner concurs that Serafini et al. or Neckers combined with Norman, does not suggest halogenated xanthenes, used with ionizing radiation as a radiosensitizer agent for enhancing radiation therapy in treating cancer or tumor. Examiner concurs that Norman teaches gandolinium as the radiosensitizer agent or iodinated contrast agent used for enhancing efficacy of radiation therapy. Examiner also concedes that gandolinium is not a halogenated xanthene. However, Rose Bengal, just like gandolinium, is an iodinated contrast agent which Serafini et al. and Neckers have characterized as being activatable. Therefore, Norman was incorporated into the teaching of Serafini or Neckers, for the teaching of activating a contrast medium at a specific ionizing radiation level, which Norman used to demonstrate that his iondinated contrast agent exhibits preference to localize in diseased tumor tissue. Alternatively, the recited claims are not drawn to a novel method of using Rose Bengal with ionizing radiation applied to cancer and tumors to increase efficacy of the radiation therapy. Instead, the claims are drawn to the halogenated xanthenes as products, specifically Rose Bengal, which Appellant admits in this Brief at page 18, first full paragraph that they are known substances in the art. The teaching of the combination of Serafini or Neckers with Norman, albeit silent in suggesting capacity of a halogenated xanthene to enhance radiation therapy upon application of ionizing radiation, nevertheless, suggests irradiating an imaging contrast agent such as gandolinium at a specific radiation level and that halogenated xanthenes are a variation of imaging contrast agents, that should interact with ionizing radiation for activation in radiation therapy at a specific ionization level, i.e. 140 keV.

In sum, Appellant has, indeed, discovered that halogenated xanthenes such as Rose Bengal, can be used for treatment of cancer and tumors by activating the compounds with ionizing radiation at specific levels, by interacting with the ionizing radiation applied into the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation. Appellant's allowed application, ASN 09/216,787, now US 6,331,286, claimed just that, and was deemed to be a novel and nonobvious method of using the halogenated xanthenes. However, the product which is a radiosensitizer agent comprising halogenated xanthene, has not been deemed nor defined to be structurally distinct from the product that is currently known in the art. To reiterate, the discovery of a new property of known product, in this case, halogenated xanthenes such as Rose Bengal, discovered to characteristically enhance efficacy of ionizing radiation applied to cancer or tumor in radiation therapy, does not render the product novel, unless otherwise, rendered novel or nonobvious from a modification or variation of its original structure, i.e. "ionized Rose Bengal" or "derivatized Rose Bengal with a biological targeting moiety", that is structurally different, novel, and nonobvious, i.e. with different pH (as an example) from all other commercially known Rose Bengal. The recitation of the intended use of the claimed invention must also result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Gailene R. Gabel
July 18, 2002

Conferees

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James Housel, AU 1648